PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Sojiro SHIOKAWA, *et al.*

Docket No: Q64460

Appln. No.: 09/856,372

Group Art Unit: 1624

Confirmation No.: 8305

Examiner: Brenda Libby COLEMAN

Filed: November 2, 2001

For: BENZOXAZOLE DERIVATIVES AND MEDICAMENTS COMPRISING SAID DERIVATIVES AS ACTIVE INGREDIENT

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Yasuo SATO, hereby declare and state:

THAT I am a citizen of Japan;

THAT I graduated from The University of Tokyo, Faculty of Pharmaceutical Science, in March 1985, received a Master's degree from The University of Tokyo in March 1987, and received the degree of Doctor of Philosophy (pharmaceutical science, especially organic and medicinal chemistry) from The University of Tokyo in May 1995.

THAT I have been employed by Meiji Seika Kaisha, Ltd. since April 1987, where I have been engaged in the research and development of new drugs; and

THAT I am familiar with the prosecution of the above-identified U.S. patent application, including the Office Action mailed April 28, 2005.

I conducted experiments to demonstrate the unexpectedly superior results of the presently claimed invention over the following comparative compounds: 5-chloro-7-methyl-2-piperazinyl benzoxazole (Comparative Compound F disclosed in Test Example of the specification); and

5,7-dimethyl-2-homopiperazinyl benzoxazole (a newly prepared comparative compound, referred to below as Comparative Compound H).

Preparation of Comparative Compound H

2,4-Dimethylphenol (3 ml) was dissolved in a mixture of diethyl ether (40 ml) and water (40 ml), and the mixture was added with concentrated hydrochloric acid (8 ml), and then, further added with sodium nitrate (2.71 g) under ice cooling. After the mixture was stirred at room temperature for 3 hours, the reaction mixture was diluted with n-hexane (40 ml). The organic layer was separated and washed successively with water (50 ml) and saturated brine (50 ml), and then the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain 2,4-dimethyl-6-nitrophenol (3.38 g) as yellow crystals.

The above product (700 mg) was dissolved in ethanol (8 ml) and added with palladium on charcoal (10%, 70 mg) and the atmosphere was replaced with hydrogen gas at room temperature. The mixture was stirred for 4 hours. The palladium catalyst was removed from the reaction mixture by filtration, and the filtrate was added with absolute ethanol (10 mL), carbon disulfide (5 ml), and potassium hydroxide (175 mg) and stirred and heated under reflux for about 6 hours. The solvent was removed under reduced pressure, and the residue was dissolved in water (20 ml) and the solution was adjusted to a pH below 7 using 5N hydrochloric acid. The precipitates were collected and dried in vacuo in a desiccator to obtain 5,7-dimethyl-2-mercaptobenzoxazole (2.4 g).

The resulting product (200 mg) was suspended in toluene (10 ml) and added with homopiperazine (220 mg) and the mixture was heated under reflux for 6 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 ml) and water (10 ml). The pH of the mixture was adjusted to 7.5 by dropwise addition of 5N hydrochloric acid with stirring, and the organic layer separated was washed with water (20 ml). The organic layer was further added with water (20 ml) and the pH of the mixture was adjusted to 1 to 1.5 using 5N hydrochloric acid, and then the layers were separated. The aqueous layer was added with ethyl acetate (20 ml) and adjusted to pH 8.0 using 5N aqueous solution of sodium

hydroxide, and the organic layer separated was dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to obtain the target compound.

^{1}H-NMR ($CDCL_3$) δ : 1.95 (2H, m), 2.34 (3H, s), 2.37 (3H, s), 2.91 (2H, m), 3.07 (2H, m), 3.75-3.83 (4H, m), 6.61 (1H, m), 6.97 (1H, m).
MS (FAB) m/z : 246 (M+1).

Tests

Test for 5-HT_3 receptor activating action (Test 1) was carried out according to Test Example 1 of the specification. 5-HT_3 receptor binding assay (Test 2) was carried out according to the method described as "5-HT_3 Receptor Binding Assay" in right column on page 3020 of J. Med. Chem., 1998, Vol. 41, No. 16, pp. 3015-3021. For Comparative Compound H, experiments were repeated twice. Test for inhibitory action for rat diarrhea under restriction stress (Test 3) was carried out according to Test Example 2 of the specification. For Comparative Compound H, this test was omitted because the compound gave very poor results in the above two experiments. Results obtained are shown below.

Test 1 - Contraction Test of Guinea Pig Ileum

	Compound H	Compound F	Compound Ex. 1(b)
pD2	6.82	7.56	7.48
i.a.	0.13	0.14	0.12
5-HT_3 antagonist (10 μM, %)	81	90	95

Test 2 - Receptor Binding Assay

	Compound H	Compound F	Compound Ex. 1(b)
Rat Ki (nM)	240	14.2	4.6

Test 3 - Inhibition of Rat Stress Induced Diarrhea

	Compound H	Compound F	Compound Ex. 1(b)
ED_{50} (mg/kg)	Not tested	0.052	0.00025

From the above, it is clear that the presently claimed compound has unexpectedly superior effects over the structurally similar compounds falling within the scope of the claims of U.S. Patent Nos. 6,037,342, 6,867,226, and 6,552,057.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 09/06/2005

Yasuo Sato

Dr. Yasuo SATO